Matthew B. Van Hook
DEPUTY GENERAL COUNSEL

PhRMA

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Dockets Management Branch
[HFA-305]
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments On FDA Draft Guidance for Industry: *Information Request and Discipline Review Letters Under the Prescription Drug User Fee Act (PDUFA),* 64 *Fed. Reg.* 44741 (August 17, 1999), Docket No. 99D-2405

Dear FDA:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing $24 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

An overarching goal of both the innovator pharmaceutical industry, and FDA, is to identify and implement means to provide safe and effective medicines to patients sooner. Congress provided significant new resources to FDA to accomplish this mutual goal in 1992, with the establishment of a user fee program aimed at providing additional funds earmarked for improving the drug review and approval process. Over the first five years of the program (PDUFA-1), FDA was able to utilize $327 million in industry-provided funds beyond the baseline provided by Congress for the review and revision of new drug applications, and hired 600 additional chemists to assist in the review process. PDUFA-I proved to be an unqualified success, with FDA meeting all of its related performance goals, resulting in a reduction of average drug review times from 30 months to 15.5 months. For this achievement, the FDA deservedly won the prestigious Innovations In American Government Award in late 1997.

PDUFA-II continues to build on this record of success. With the extended and enhanced resources provided by PDUFA-II, FDA has also agreed to a range of new performance goals which together, and by the completion of PDUFA-II at the end of FY2000, are expected to reduce overall drug development and review time by 10 to 16

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1100 Fifteenth Street, NW, Washington, DC 20005 • Tel: 202-835-3513 • FAX: 202-835-3592 • E-MAIL: mvanhook@phrma.org

months, including a reduction in review times for standard applications from 12 months to 10 months. As with PDUFA-I, these performance goals are referenced in the FDA Modernization (FDAMA) legislation that included the reauthorization of PDUFA, and were memorialized in their entirety as an appendix to letters from Health and Human Services Secretary Shalala to the House and Senate Leadership (see Congressional Record of November 13, 1997, pp. H10887-H10889).

The performance goal that occasioned the above-referenced draft Guidance for Industry is set forth under Section VIII *Additional Procedures*:

> B. *Timing of sponsor notification of deficiencies in applications*
> "To help expedite the development of drug and biologic products, CBER and CDER intend to submit deficiencies to sponsors in the form of an 'information request' (IR) letter when each discipline has finished its initial review of its section of the pending application." PDUFA-II Performance Goals, VIII.B., Congressional Record of November 13, 1997, p. H10889 column 1.

PhRMA appreciates this opportunity to comment on the draft Guidance For Industry, and supports the approach in the Guidance of identifying the letters relating to deficiencies in applications following the completion of review by particular disciplines as **"Discipline Review (DR)"** letters. PhRMA also supports the decision to continue the pre-existing practice of issuing **"Information Request (IR)"** letters, which request information while a specific discipline review is in progress. Set forth below are four specific comments on the draft Guidance.

1. **Guidance Should Apply To All Applications, Including Supplements**

The first paragraph of the INTRODUCTION section states that information request (IR) letters and discipline review (DR) letters do not apply to supplemental applications or resubmissions. This is inconsistent not only with the spirit/intention of PDUFA but also with the language of the goal document provided by the Secretary of Health and Human Services to the Chairman of the Committee on Labor and Human Resources on November 12, 1997. Section VIII.B. of the goals document states:

> "To help expedite the development of drug and biologic products, CBER and CDER intend to submit deficiencies to sponsors in the form of an "information request" (IR) letter when each discipline has finished its initial review of its section of the pending application. (underline added)"

Throughout the goals document, the Secretary distinguishes between elements that are applicable to "original applications" (i.e. does not include supplements or resubmissions) and "pending applications" (i.e. does include supplements and resubmissions). Thus, it is clear that the Secretary's commitment regarding DR letters

applies to original applications, supplements, and resubmissions and the Guidance should be revised accordingly.

2. **Differences Between Discipline Review (DR) and Information Request (IR) Letters**

The first paragraph of Section IV.A. of the Guidance contains general statements about the issuance and use of IR and DR letters. Some of these statements need to be revised to reflect differences in the nature of IR and DR letters, the fact that IR and DR letters apply to supplements, and the fact that the concept of the major amendment/extended review cycle applies only to original applications. Specifically:

- the guidance states "However, if the response is of a significant nature, the response could constitute a major amendment." The guidance should be revised to indicate that this statement applies only to sponsor responses to original applications.

- the guidance states "Review of a response may be deferred to the next review cycle." The guidance should be revised to specify that this comment applies only to responses to DR letters and not responses to IR letters which, depending on their size/complexity can trigger extension of the review clock in the case of original applications.

3. **The Presumption Is That Discipline Review (DR) Letters Should Be Provided To The Sponsor**

The second paragraph of Section IV.A. contains the statements "CBER and CDER will generally (underline added) convey early thoughts on possible deficiencies..." and "A DR letter will be used... only if (underline added) , in the Division's judgment, it is efficient to do so (underline added)." These statements are inconsistent with the Secretary's commitment (Section VIII.B.) which states "To help expedite the development of drug and biologic products, CBER and CDER intend to submit (underline added) deficiencies to sponsors...." Thus this section of the guidance should be revised, consistent with the Secretary's commitment, to reflect the expectation that DR letters will be provided unless, as is stated in Section II, "...the discipline review completes the review of the application" (i.e. a complete response or approval letter would be issued).

4. **Differential Effects Of Discipline Review (DR) and Information Request (IR) Letters On The User Fee Clock**

The first paragraph of Section IV.B. contains statements regarding the effect of applicant responses to IR and DR letters on the user fee clock. These statements are confusing, and in some cases incorrect, as a result of not recognizing the differences

between IR and DR letters and/or not specifying which statements apply to which type of letter. Specific issues are indicated below:

- The second sentence of this paragraph which reads "Normally, unless the amount and type of information is substantive or voluminous, the view of a clarifying IR letter response will occur during the current review cycle" is incorrect in that responses to IR letters must be reviewed during the review cycle, albeit with an extension of the review cycle in the case of original applications. This statement would be correct in the context of a DR letter which the Agency is not obligated to review upon receipt.

  Likewise, sentences four, five, and six should be revised to indicate that they specifically refer to responses to DR letters.

- The third sentence of this paragraph should be modified to read "A response to a DR letter conveying deficiencies identified in a discipline review ***of an original application*** may or may not be considered a major amendment which would extend the review time for the current cycle." This change recognizes the fact that extension of the review clock in response to a major amendment is only applicable to original applications.

* * *

PhRMA appreciates the opportunity to comment on this draft Guidance For Industry. The proper use of IR and DR letters under the Prescription Drug User Fee Act will permit review issues to be resolved expeditiously, and thereby serve to bring new medicines to waiting patients sooner, as intended by Congress in PDUFA-II.

Sincerely,

Matthew B. Van Hook

cc: Murray M. Lumpkin, CDER (HFD-2)
Robert A. Yetter, CBER (HFM-10)